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(54) Title: THERAPY FOR IMPROVING COGNITION

(57) Abstract

The present invention is concerned with pharmaceutical compositions comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

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THERAPY FOR IMPROVING COGNITION

The present invention is concerned with pharmaceutical compositions comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias, or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

Of particular interest is the use of an atypical antipsychotic agent (I) for the preparation of a medicament for reducing adverse effects associated with acetylcholinesterase inhibitors (II) in patients suffering from Alzheimer's disease or related dementias, such as nausea, vomiting, sweating, restlessness and insomnia. Especially interesting is the use of an atypical antipsychotic agent (I) for the preparation of a medicament for improving sleep in patients suffering from Alzheimer's disease or related dementias while being treated with acetylcholinesterase inhibitors (II).

The present invention is concerned with a pharmaceutical composition comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias, or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

The atypical antipsychotic (I) is selected from risperidone, 9-hydroxyrisperidone or a C_{10-20} alkanoic acid ester thereof, olanzapine, quetiapine, iloperidone or ziprasidone, and the acetylcholinesterase inhibitor (II) is selected from galantamine, rivastigmine or donepezil, or therapeutically active acid addition salt form of any of the foregoing. Said salts comprise salt forms which the active ingredients (I) and (II) are able to form with appropriate acids, such as, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or

organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pamoic and the like acids. For example, galantamine may conveniently be used as the (1:1) hydrobromide salt.

C_{10-20}alkanoic acids are selected from the group consisting of decanoic (capric), undecanoic, dodecanoic (lauric), tridecanoic, tetradecanoic (myristic), pentadecanoic, hexadecanoic (palmitic), heptadecanoic, octadecanoic (stearic), nonadecanoic and eicosanoic acid. Due to their limited aqueous solubility, it was generally believed that the esters had to be suspended into oils. The ester having a C_{15} (pentadecyl) chain and the active ingredient corresponding thereto being the 9-hydroxyrisperidone palmitate ester was found to be the superior ester from a pharmacokinetic, as well as from a tolerance point of view.

Preferably, the amount of each of the active ingredients is equal to or less than that which is approved in monotherapy with said active ingredient.

Most preferred are compositions wherein the atypical antipsychotic (I) is risperidone and the acetylcholinesterase inhibitor (II) is galantamine, in particular as galantamine hydrobromide. In said compositions, the amount of risperidone is 0.5, 1, 2, 4, or 6 mg and that of galantamine (as base) is 8, 16, 24 or 32 mg per dosage form.

The present invention also relates to products containing as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), as combined preparations for simultaneous, separate or sequential use in the treatment of patients suffering from psychosis, Alzheimer's disease or related dementias.

The present invention also concerns the use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for enhancing the effect of an atypical antipsychotic agent (I) on cognition in patients suffering from psychosis.

Conversely, the present invention also concerns the use of an atypical antipsychotic agent (I) for the preparation of a medicament for enhancing the effect of an acetylcholinesterase inhibitor (II) on cognition in patients suffering from Alzheimer's disease or related dementias.

Additionally, the present invention concerns the use of an atypical antipsychotic agent (I) for the preparation of a medicament for reducing adverse effects associated with acetylcholinesterase inhibitors (II) in patients suffering from Alzheimer's disease or related dementias. Said adverse effect can be nausea, vomiting, sweating, restlessness or insomnia. Especially interesting is the use of an atypical antipsychotic agent (I) for the preparation of a medicament for improving sleep in patients suffering from Alzheimer's disease or related dementias while being treated with acetylcholinesterase inhibitors (II).

Finally, the present invention also concerns the use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for reducing adverse effects associated with atypical antipsychotic agents (I) in patients suffering from psychoses. Said the adverse effect can be extrapyramidal syndrome or tardive dyskinesia.

In all the preceding uses the atypical antipsychotic (I) is preferably risperidone and the acetylcholinesterase inhibitor (II) is preferably galantamine, in particular the (1:1) hydrobromide.

Claims

1. A pharmaceutical composition comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, Alzheimer's disease or related dementias.

2. A composition according to claim 1 wherein said therapeutically beneficial effect is a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias, or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

3. A composition according to claim 1 wherein the atypical antipsychotic (I) is selected from risperidone, 9-hydroxyrisperidone or a C_{10-20} alkanoic acid ester thereof, olanzapine, quetiapine, iloperidone or ziprasidone, and the acetylcholinesterase inhibitor (II) is selected from galantamine, rivastigmine or donepezil.

4. A composition according to claim 3 wherein the amount of each of the active ingredients is equal to or less than that which is approved in monotherapy with said active ingredient.

5. A composition according to claim 3 wherein the atypical antipsychotic (I) is risperidone and the acetylcholinesterase inhibitor (II) is galantamine.

6. A composition according to claim 5 wherein the amount of risperidone is 0.5, 1, 2, 4, or 6 mg and that of galantamine (as base) is 8, 16, 24 or 32 mg per dosage form.

7. A product containing as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from psychosis, Alzheimer's disease or related dementias.

8. The use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for enhancing the effect of an atypical antipsychotic agent (I) on cognition in patients suffering from psychosis.

9. The use of an atypical antipsychotic agent (I) for the preparation of a medicament for enhancing the effect of an acetylcholinesterase inhibitor (II) on cognition in patients suffering from Alzheimer's disease or related dementias.

10. The use of an atypical antipsychotic agent (I) for the preparation of a medicament for reducing adverse effects associated with acetylcholinesterase inhibitors (II) in patients suffering from Alzheimer's disease or related dementias.

11. Use according to claim 10 wherein the adverse effect is nausea, vomiting, sweating, restlessness or insomnia.

12. The use of an acetylcholinesterase inhibitor (II) for the preparation of a medicament for reducing adverse effects associated with atypical antipsychotic agents (I) in patients suffering from psychoses.

13. Use according to claim 12 wherein the adverse effect is extrapyramidal syndrome or tardive dyskinesia.

14. Use according to any one of claims 8 to 13 wherein the atypical antipsychotic (I) is risperidone and the acetylcholinesterase inhibitor (II) is galantamine.

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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Patent Department, Turnhoutseweg 30, B–2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DE NIJS, Paul, Leonce, Irma [BE/BE]; (BE). PARYS, Wim, Louis, Julien [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B–2340 Beerse (BE).

(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Department – ext. 3547, Turnhoutseweg 30, B–2340 Beerse (BE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
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27 July 2000 (27.07.00)

(54) Title: ATYPICAL ANTIPHSYCHOTIC IN COMBINATION WITH ACETYLCHOLINESTERASE INHIBITOR FOR IMPROVING COGNITION

(57) Abstract

The present invention is concerned with pharmaceutical compositions comprising a carrier and as first active ingredient an atypical antipsychotic agent (I) and as second active ingredient an acetylcholinesterase inhibitor (II), each in an amount producing a therapeutically beneficial effect in patients suffering from psychosis, or Alzheimer's disease or related dementias. Said therapeutically beneficial effect can be a synergistic effect on the cognitive functioning of patients suffering from Alzheimer's disease or related dementias or the prevention of the further deterioration of cognition in said patients, or the reduction of adverse effects associated with the one of the active ingredients by the other of the active ingredients.

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/07804

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP 0 879 596 A (SNORASSON ERNIR) 25 November 1998 (1998-11-25) abstract; claims 37,38 page 3	1-14
X	EP 0 515 301 A (SNORRASON ERNIR) 25 November 1992 (1992-11-25) abstract page 3; claim 39	1-14
E	WO 99 52519 A (GEN HOSPITAL CORP) 21 October 1999 (1999-10-21) claims 34,37,38	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2000	26/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gonzalez Ramon, N

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 07378 A (SANBERG PAUL RONALD ;SHYTLE ROLAND DOUGLAS (US); SILVER ARCHIE AAR) 18 February 1999 (1999-02-18) abstract page 8 -page 9; claim 11	1-16
X,P	FERNANDEZ H.H. ET AL: "Donepezil for Huntington's disease." MOVEMENT DISORDERS, (2000) 15/1 (173-176). , XP000892632 table 1	1-16
X,P	GALASKO D: "A CLINICAL APPROACH TO DEMENTIA WITH LEWY BODIES" THE NEUROLOGIST, vol. 5, no. 5, September 1999 (1999-09), pages 247-257, XP000878694 abstract; table 4 page 255, column 2	1-16
Y,P	KELLY J S: "Alzheimer's disease: the tacrine legacy" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 20, no. 4, April 1999 (1999-04), pages 127-129, XP004172560 ISSN: 0165-6147 the whole document	1-16
X	GEIZER M. ET AL: "Combination of risperidone and donepezil in Lewy body dementia" CAN. J. PSYCHIATRY,May 1998 (1998-05), pages 421-422, XP000892680 the whole document	1-16
T	MAZUREK A. A.: "Treatment of Alzheimer's disease" N ENG J. MED, vol. 342, no. 11, 16 March 2000 (2000-03-16), pages 821-822, XP000901026 page 821, column 2, paragraph 1	1-16
X,P	YAQUB B.A.: "New horizons in management of Alzheimer 's disease." SAUDI MEDICAL JOURNAL, (1999) 20/9 (671-677). , XP000892838 page 672 -page 673; table 1	1-16

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y,P	MELTZER, H. Y. (1) ET AL: "Atypical antipsychotic drugs (APD) but not typical APD increased extracellular acetylcholine (ACh-ext) levels in rat medial prefrontal cortex (mPFC) in the absence AChEsterase (AChE) inhibition." SOCIETY FOR NEUROSCIENCE ABSTRACTS, (1999) VOL. 25, NO. 1-2, PP. 452. MEETING INFO.: 29TH ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, PART 1 MIAMI BEACH, FLORIDA, USA OCTOBER 23-28, 1999 THE SOCIETY FOR NEUROSCIENCE. , XP000892699 abstract	1-16
X	MAGNUSON T M ET AL: "Extrapyramidal side effects in a patient treated with risperidone plus donepezil 'letter!." AMERICAN JOURNAL OF PSYCHIATRY, (1998 OCT) 155 (10) 1458-9. , XP000892634 the whole document	1-16
X	SIMONSON W.: "Promising agents for treating Alzheimer's disease." AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (1 NOV 1998) 55/21 SUPPL. (S11-S16). , XP002134583 page S14, column 2, paragraph 3	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/ 07804

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,7-13
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
SEE FURTHER INFORMATION SHEET PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,7-13

Present claims 1,2,7-13 relate to compounds defined by reference to the following parameters: "atypical antipsychotic agent" and "acetylcholinesterase inhibitor".
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specifically disclosed in the examples and the claims with due regard to the general idea underlying the present application

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/EP 99/07804

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0879596 A	25-11-1998	AT 178791 T	15-04-1999
		AU 663086 B	28-09-1995
		AU 1873692 A	30-12-1992
		AU 1886392 A	30-12-1992
		CA 2062094 A	15-11-1992
		CA 2103022 A	15-11-1992
		DE 69228928 D	20-05-1999
		DE 69228928 T	28-10-1999
		WO 9220328 A	26-11-1992
		EP 0515302 A	25-11-1992
		EP 0584285 A	02-03-1994
		ES 2129450 T	16-06-1999
		GR 3030046 T	30-07-1999
		JP 6507621 T	01-09-1994
		NO 934103 A	12-11-1993
		NO 983939 A	12-11-1993
		NZ 242743 A	24-02-1997
		US 5589475 A	31-12-1996
		US 5633238 A	27-05-1997
		US 5336675 A	09-08-1994
		AT 183084 T	15-08-1999
		AU 658424 B	13-04-1995
		CA 2108880 A	15-11-1992
		DE 69229781 D	16-09-1999
		DE 69229781 T	05-01-2000
		WO 9220327 A	26-11-1992
		EP 0515301 A	25-11-1992
		EP 0584185 A	02-03-1994
		ES 2134215 T	01-10-1999
		GR 3031559 T	31-01-2000
		JP 6507617 T	01-09-1994
		NO 934104 A	12-11-1993
		NZ 242744 A	24-02-1997
		US 5312817 A	17-05-1994
		ZA 9203505 A	24-02-1993
		ZA 9203506 A	24-02-1993
EP 0515301 A	25-11-1992	AT 183084 T	15-08-1999
		AU 1873692 A	30-12-1992
		AU 658424 B	13-04-1995
		AU 1886392 A	30-12-1992
		CA 2108880 A	15-11-1992
		DE 69229781 D	16-09-1999
		DE 69229781 T	05-01-2000
		WO 9220327 A	26-11-1992
		EP 0584185 A	02-03-1994
		ES 2134215 T	01-10-1999
		GR 3031559 T	31-01-2000
		JP 6507617 T	01-09-1994
		NO 934104 A	12-11-1993
		NZ 242744 A	24-02-1997
		US 5312817 A	17-05-1994
		AT 178791 T	15-04-1999
		AU 663086 B	28-09-1995
		CA 2062094 A	15-11-1992
		CA 2103022 A	15-11-1992
		DE 69228928 D	20-05-1999
		DE 69228928 T	28-10-1999

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter onal Application No
PCT/EP 99/07804

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0515301 A		WO 9220328 A	26-11-1992
		EP 0515302 A	25-11-1992
		EP 0584285 A	02-03-1994
		EP 0879596 A	25-11-1998
		ES 2129450 T	16-06-1999
		GR 3030046 T	30-07-1999
		JP 6507621 T	01-09-1994
		NO 934103 A	12-11-1993
		NO 983939 A	12-11-1993
		NZ 242743 A	24-02-1997
		US 5589475 A	31-12-1996
		US 5633238 A	27-05-1997
		US 5336675 A	09-08-1994
		ZA 9203505 A	24-02-1993
		ZA 9203506 A	24-02-1993
WO 9952519 A	21-10-1999	AU 3557199 A	01-11-1999
WO 9907378 A	18-02-1999	AU 2118499 A	01-03-1999
		AU 8778498 A	01-03-1999
		WO 9907356 A	18-02-1999
		US 6034079 A	07-03-2000